Remarks

With entry of the amendment, claims 15-23 are pending. Claims 1-14 have been cancelled, and claims 15-23 are newly added. The amendments introduce no new matter and are fully supported by the specification as indicated below.

Support for claim 15 is found at least in claims 1 and 4, as originally filed, at page 8, lines 30-35 of the specification, and at page 23, line 24-page 24, line 24 of the specification.

Support for claim 16 is found at least in claim 1, 3, and 4, as originally filed.

Support for claim 17 is found at least at claims 1, 3, and 4, and at page 24, lines 20-24 of the specification.

Support for claim 18 is found at least at claims 1, 3, 4, and 6 as originally filed.

Support for claim 19 is found at least at claims 1, 3, 4, 6, and 7 as originally filed.

Support for claim 20 is found at least at claims 1, 3, 4, and 6-8 as originally filed.

Support for claim 21 is found at least at claims 1, 3, 4, 6-8, and 11 as originally filed.

Support for claim 22 is found at least at 1, 4, and 11 as originally filed.

Support for claim 23 is found at least at 1, 4, 11, and 12 as originally filed.

In view of the amendments above and the arguments below, Applicants respectfully request allowance of the claims.

Priority

Applicants have amended the Statement Regarding Related Applications to reflect that the instant application is a continuation of US Application No. 09/398,385, consistent with the information provided in the transmittal letter submitted with the application at the time of filing and as reflected on the Official Filing Receipt.

Rejections under 37 C.F.R. 112, second paragraph

Claims 1 and 6-12 are rejected as being indefinite for the recitation of "a structurally analogous sequence". Claims 1 and 6-12 have been cancelled, and none of new claims 15-23 includes that limitation. Thus, Applicants request withdrawal of the rejection.

Rejections under 35 U.S.C. 102(b)

Claims 1, 11, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,641,650 (the '650 patent). The '650 patent is characterized as disclosing a

bacteriorhodopsin protein amino acid sequence (the signal sequence or C-terminal sequence) in which the remaining part of the bacteriorhodopsin (i.e., "at least a portion") was replaced with the structurally analogous region of a G-protein receptor protein. The '650 patent is also cited as purportedly teaching a method of producing a chimeric protein according to claims 11 and 12.

Applicants have cancelled claims 1, 11, and 12, thus rendering moot this rejection. Applicants respectfully submit that claims 15-24 are not anticipated by the '650 patent, in that the '650 patent fails to teach each and every limitation of any of claims 15-24.

Rejections under 35 U.S.C. 103(a)

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.* (Current Opinion in Biotechnology 6:394-402, 1995), Hoflack *et al.* (Trends in Pharm. Sci. 15:7-9, 1994), Teufel *et al.* (EMBO J. 12:3399-3408, 1993), in view of Okamoto *et al.* (Cell 67:723-730, 1991).

Popot *et al.* is cited as suggesting that chimeric constructs of bacteriorhodopsin and GPCRs can be made for use in functional and structural investigations, and as teaching that bacteriorhodopsin can be used as a "benchtop" to arrange engineered loops (p. 397, col. 2). Popot is further characterized as teaching that cytoplasmic loop III can be cut without preventing refolding (e.g., cytoplasmic loop III, Teufel *et al.*). Hoflack *et al.* purportedly reflects that it is "old and well established that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors". Teufel is cited as teaching that the BR can be used as a structural scaffold to construct biological membranes with new and predefined properties by replacing extra-membrane parts of BR with exogenous polypeptide modules. Citing to p. 3405, last paragraph of Teufel *et al.*, the Examiner further characterizes Teufel *et al.* as teaching that loops B/C, C/D, D/E, and E/F are prime candidates for constructing loop replacements, and as defining the third cytoplasmic loop as corresponding to amino acids 171-179 of SEQ ID NO:2. Okamoto is said to teach that peptides corresponding to the third cytoplasmic loop of a GPCR (e.g., human β-adrenergic receptor) can activate G-protein. Hoflack is also cited as teaching that pharmaceutical companies use BR as a template to model G-protein coupled receptors in drug design.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established for the claimed invention. A *prima facie* case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) the art reference or combination of references must teach all of the claim limitations (MPEP 2142). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143).

The art of record does not combine to teach or suggest all of the limitations of new claims 15-23. Claims 15-17 are drawn to a chimeric fusion protein in which a portion of the intracellular loop three domain of bacteriorhodopsin is replaced by a portion of the intracellular loop three domain of bovine rhodopsin, the protein having the ability to promote *in vitro* GTP-GCP exchange on tranducin; claims 18-20 are drawn to polynucleotide sequences encoding the protein of claim 17, in which the replacement region is specifically recited; and claims 21-23 are drawn to methods employing the chimeric protein of claim 15. Furthermore, there is no motivation to modify the prior art teachings to make the claimed invention, nor does the prior art provide a reasonable expectation of success. Applicants emphasize that Applicants' disclosure represents the first report of a chimeric bacteriorhodopsin/G-protein coupled receptor having the ability to promote GTP-GDP exchange on a G protein.

Hoflack calls into question whether bacteriorhodopsin is a valid model for studying the three dimensional structures of G protein-coupled receptors, given differences in electron diffraction maps of bovine rhodopsin and bacteriorhodopsin, which may be attributable to differences in packing the α helices. As the Examiner pointed out at pages 4 and 5 of the Office Action in the rejection of cancelled claims 1-14 under 35 CFR 112, Hoflack teaches that the art is equivocal as to the precise structural relationships between bacteriorhodopsin and G-protein coupled receptors, in that the transmembrane regions of bacteriorhodopsin and G-protein coupled receptors do not correspond to each other and available structural data suggest that bacteriorhodopsin and rhodopsin have clear differences in the packing of the helices. Accordingly, the cited art does not provide a reasonable expectation of success.

Teufel *et al.* taught replacing specific regions of bacteriorhodopsin with a Sendai virus peptide to form a chimeric bacteriorhodopsin. Chimeras in which B/C, C/D, D/E, or E/F loops were replaced retained bacteriorhodopsin function. Two chimeras, including one in which the 13 amino acid viral peptide was inserted into the E/F loop (i.e., intracellular loop three domain), retained the viral peptide "function" (i.e., the ability to bind to a monoclonal antibody directed against the viral peptide). Applicants respectfully submit that although B/C, C/D, D/E, or E/F loops may have been identified as "prime candidates for future constructions", there is no suggestion in Teufel et al, either alone or in combination with the other cited references, to replace any of these loops with the intracellular loop three domain of bovine rhodopsin. Furthermore, that a chimeric bacteriorhodopsin in which the E/F loop was replaced with a viral peptide was able to bind an antibody to the viral peptide is not predictive of the ability of a chimeric bacteriorhodopsin according to the presently claimed invention to promote *in vitro* GTP-GDP exchange on transducin.

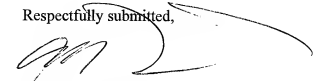
Okamato *et al.* reported that a soluble synthetic peptide having amino acid residues 259-273 of the β-adrenergic receptor (βIII-2 peptide) was sufficient to promote GTPγS binding to G_S; however, there is no suggestion to develop a bacteriorhodopsin chimera in which a portion of the intracellular loop 3 domain is replaced by at least a portion of the intracellular loop 3 domain of bovine rhodopsin, let alone a reasonable expectation that the protein would promote *in vitro* GTP-GDP exchange on transducin. Applicants submit that although Okamato may provide motivation to further study the intracellular loop 3 region of the β-adrenergic receptor, Okamato does not provide motivation to accomplish that objective by modifying Popot, Hoflack, and Teufel *et al.* In fact, Okamato suggests that the goal of further characterizing the β-adrenergic receptor may be accomplished using the relatively simple βIII-2 peptide.

In light of the foregoing, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Please charge $225.00 for the two-month extension of time fee to Deposit Account No. 50-0842. No other fee is believed due. However, if a fee is owing, please charge Deposit Account No. 50-0842 for such fee.

Should Examiner Brannock feel that any other point requires consideration or that the form of the claims can be improved, he is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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